REMARKS

Reconsideration of this application is respectfully requested.

35 U.S.C. §101 - Utility

Claims 51-54 and 57 stand rejected under 35 U.S.C. §101, allegedly because the claimed invention is not supported by a substantial asserted utility or a well-established utility. (Office Action at 2, paragraph 4.) Specifically, the Office states that:

> The specification suggests but does not demonstrate that the claimed polypeptides have GDP-D-mannose dehydratase activity based on a 51% homology with a GDP-D-mannose dehydratase from another organism. Neither the specification or the art describe the significance of this activity or a real world use for a protein with this activity.

(*Id.*)

Applicant courteously disagrees with the Office and respectfully submits that if the Office rejects claims for failing to comply with the utility requirement, it must also provide a technical reason why the rejection is being made. The MPEP, at 2154.07 I.B., states:

> When the [E]xaminer concludes that an application is describing an invention that is nonuseful, inoperative, or contradicts known scientific principles, the burden is on the [E]xaminer to provide a reasonable basis to support this conclusion.

Applicant respectfully submits that the Office has not offered a technical reason for the allegation that the claimed invention lacks utility. Moreover, the Office has overlooked the specification's teachings that relate to the established utility of the claimed invention.

More to the point, Applicant respectfully submits that one of skill in the art would have understood the utility of the claimed invention based on the significant similarity of the polypeptide of the invention to GDP-D-mannose dehydratase, because of common knowledge in the art that variations in the polysaccharide compositions of bacterial cell walls among different species are likely due to differences in the expression of polysaccharide processing enzyme activity, such as GDP-D-mannose dehydratase. In fact, the specification emphasizes this point at paragraph 63 as part of a discussion related to the gene that encodes the polypeptide of the invention and is deleted in *M. bovis* BCG, but not *M. tuberculosis*.

> As polysaccharide is a major constituent of the mycobacterial cell wall, these deleted genes may cause the cell wall of *M. bovis* BCG to differ from that of *M. tuberculosis*, a fact that may have important consequences for both the immune response to *M. bovis* BCG and virulence. Detection of such a polysaccharide is of diagnostic interest and possibly useful in the design of tuberculosis vaccines.

Thus, in view of the above excerpt from the specification, and because the polypeptide of the invention is expressed by *M. tuberculosis*, but not *M. bovis* BCG, which the specification teaches are otherwise closely related species that are distinguished from each other by their respective cell wall polysaccharide compositions, Applicant respectfully submits that one of skill in the art would have understood that the polypeptide of the invention would have utility to distinguish *M. bovis* BCG from *M. tuberculosis*.

In response to the Office's allegation that the specification did not demonstrate that the polypeptide of the invention had GDP-D mannose dehydratase activity, Applicant respectfully submits that one of skill in the art would have understood that

there was ample identity between the polypeptide of the invention and *P. aeruginoso* GDP-D-mannose dehydratase to support the expectation that the claimed peptide had dehydratase activity. Applicant respectfully requests that the Office consider the enclosed excerpt from Alberts, B. *et al.*, *The Molecular Biology of the Cell* (New York, NY: Garland Science, 4th ed. (2002), p. 144-145, under the heading "Sequence Homology Searches Can Identify Close Relatives," the authors state: "Generally speaking, a 30% identity in the sequence of two proteins is needed to be certain that a match has been found." Thus, Applicant courteously submits that one of skill in the art would have reasonably concluded that the polypeptide encoded by the polynucleotide of the invention would have possessed GDP-D-mannose dehydratase enzymatic activity, and the utility as taught in the specification.

Applicant also respectfully submits that, regardless of the function of the encoded polypeptide, one of skill in the art would have recognized that the claimed polynucleotide sequence of the invention had utility simply as a consequence of its expression by *M. tuberculosis*, but not *M. bovis* BCG. Indeed, with regard to the *M. tuberculosis*-encoded region encompassing the claimed polynucleotide, this point is emphasized by the specification in an excerpt which states:

> More importantly, assuming that some of the gene products from this region represent proteins with antigenic properties, it could be possible to develop a test that can reliably distinguish between the immune response induced by vaccination with *M. bovis* BCG vaccine strains and infection with *M. tuberculosis* or that the products (e.g. polysaccharides) are specific immunogens.

(Specification at paragraph 72.) Thus, Applicant respectfully submits that the specification, in addition to teaching that the polypeptide encoded by the claimed

polynucleotide has utility based on its homology to GDP-D-mannose dehydratase, as discussed above, it also clearly teaches that the claimed polynucleotide has utility based on the desirability of exploiting its differential expression between *M. tuberculosis* and *M. bovis* BCG

Accordingly, Applicant respectfully submits that the rejection of Claims 51-54 and 57, under 35 U.S.C. §101, can be withdrawn.

35 U.S.C. §112, first paragraph - Enablement

Claims 51-54 and 57 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. The specific reason the Office rejected the claims is because:

> [T]he claimed invention is not supported by a substantial utility for the reason set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

(Office Action at 3, paragraph 6.)

In response, Applicant respectfully submits that the claims are fully enabled at least because of Applicant's foregoing arguments countering the Office's rejection of the claims for allegedly failing to comply with the utility requirement. Applicant bases its reasons on the specific provisions of the MPEP regarding the relationship between 35 U.S.C. §101 and §112, which reads as follows:

> Office personnel should not impose a 35 U.S.C. §112, first paragraph rejection grounded on a "lack of utility" basis unless a 35 U.S.C. §101 rejection is proper.

(MPEP 2107.01, IV) Accordingly, because the Office's reasons for rejecting the claims under 35 U.S.C. §101 have been obviated, Applicant respectfully submits that the rejection of Claims 51-54 and 57, under 35 U.S.C. §112, first paragraph, can be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: August 9, 2007

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MOLECULAR BIOLOGY OF THE CELL

fourth edition

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Front cover Human Genome: Reprinted by permission from *Nature*, International Human Genome Sequencing Consortium, 409:860–921, 2001 © Macmillan Magazines Ltd. Adapted from an image by Francis Collins, NHGRI; Jim Kent, UCSC; Ewan Birney, EBI; and Darryl Leja, NHGRI; showing a portion of Chromosome 1 from the initial sequencing of the human genome.

Chapter opener Portion of chromosome 2 from the genome of the fruit fly *Drosophila melanogaster.* (Reprinted with permission from M.D. Adams et al., *Science* 287:2185–2195, 2000. © AAAS.)

Back cover In 1967, the British artist Peter Blake created a design classic. Nearly 35 years later Nigel Orme (illustrator), Richard Denyer (photographer), and the authors have together produced an affectionate tribute to Mr Blake's image. With its gallery of icons and influences, its assembly created almost as much complexity, intrigue and mystery as the original. *Drosophila, Arabidopsis,* Dolly and the assembled company tempt you to dip inside where, as in the original, "a splendid time is guaranteed for all." (Gunter Blobel, courtesy of The Rockefeller University; Marie Curie, Keystone Press Agency Inc; Darwin bust, by permission of the President and Council of the Royal Society; Rosalind Franklin, courtesy of Cold Spring Harbor Laboratory Archives; Dorothy Hodgkin, © The Nobel Foundation, 1964; James Joyce, etching by Peter Blake; Robert Johnson, photo booth self-portrait early 1930s, © 1986 Delta Haze Corporation all rights reserved, used by permission; Albert L. Lehninger, (unidentified photographer) courtesy of The Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions; Linus Pauling, from Ava Helen and Linus Pauling Papers, Special Collections, Oregon State University; Nicholas Poussin, courtesy of ArtToday.com; Barbara McClintock, © David Micklos, 1983; Andrei Sakharov, courtesy of Elena Bonner; Frederick Sanger, © The Nobel Foundation, 1958.)

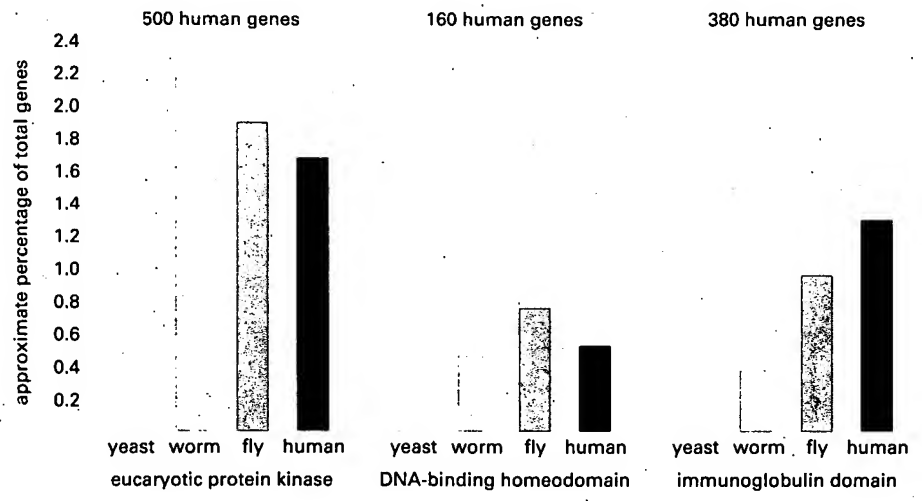

Figure 3–16 Percentage of total genes containing one or more copies of the indicated protein domain, as derived from complete genome sequences. Note that one of the three domains selected, the immunoglobulin domain, has been a relatively late addition, and its relative abundance has increased in the vertebrate lineage. The estimates of human gene numbers are approximate.

thousands of protein sequences from sequencing the genes that encode them, what technical developments can we look forward to next?

It is no longer a big step to progress from a gene sequence to the production of large amounts of the pure protein encoded by that gene. Thanks to DNA cloning and genetic engineering techniques (discussed in Chapter 8), this step is often routine. But there is still nothing routine about determining the complete three-dimensional structure of a protein. The standard technique based on x-ray diffraction requires that the protein be subjected to conditions that cause the molecules to aggregate into a large, perfectly ordered crystalline array—that is, a protein crystal. Each protein behaves quite differently in this respect, and protein crystals can be generated only through exhaustive trial-and-error methods that often take many years to succeed—if they succeed at all.

Membrane proteins and large protein complexes with many moving parts have generally been the most difficult to crystallize, which is why only a few such protein structures are displayed in this book. Increasingly, therefore, large proteins have been analyzed through determination of the structures of their individual domains: either by crystallizing isolated domains and then bombarding the crystals with x-rays, or by studying the conformations of isolated domains in concentrated aqueous solutions with powerful nuclear magnetic resonance (NMR) techniques (discussed in Chapter 8). From a combination of x-ray and NMR studies, we now know the three-dimensional shapes, or conformations, of thousands of different proteins.

By carefully comparing the conformations of known proteins, structural biologists (that is, experts on the structure of biological molecules) have concluded that there are a limited number of ways in which protein domains fold up—maybe as few as 2000. As we saw, the structures for about 1000 of these protein folds have thus far been determined; we may, therefore, already know half of the total number of possible structures for a protein domain. A complete catalog of all of the protein folds that exist in living organisms would therefore seem to be within our reach.

Sequence Homology Searches Can Identify Close Relatives

The present database of known protein sequences contains more than 500,000 entries, and it is growing very rapidly as more and more genomes are sequenced—revealing huge numbers of new genes that encode proteins. Powerful computer search programs are available that allow one to compare each newly discovered protein with this entire database, looking for possible relatives. Homologous proteins are defined as those whose genes have evolved from a common ancestral gene, and these are identified by the discovery of statistically significant similarities in amino acid sequences.

With such a large number of proteins in the database, the search programs find many nonsignificant matches, resulting in a background noise level that makes it very difficult to pick out all but the closest relatives. Generally speaking, a 30% identity in the sequence of two proteins is needed to be certain that a match has been found. However, many short signature sequences ("fingerprints") indicative of particular protein functions are known, and these are widely used to find more distant homologies (Figure 3–17).

These protein comparisons are important because related structures often imply related functions. Many years of experimentation can be saved by discovering that a new protein has an amino acid sequence homology with a protein of known function. Such sequence homologies, for example, first indicated that certain genes that cause mammalian cells to become cancerous are protein kinases. In the same way, many of the proteins that control pattern formation during the embryonic development of the fruit fly *Drosophila* were quickly recognized to be gene regulatory proteins.

Computational Methods Allow Amino Acid Sequences to Be Threaded into Known Protein Folds

We know that there are an enormous number of ways to make proteins with the same three-dimensional structure, and that—over evolutionary time—random mutations can cause amino acid sequences to change without a major change in the conformation of a protein. For this reason, one current goal of structural biologists is to determine all the different protein folds that proteins have in nature, and to devise computer-based methods to test the amino acid sequence of a domain to identify which one of these previously determined conformations the domain is likely to adopt.

A computational technique called threading can be used to fit an amino acid sequence to a particular protein fold. For each possible fold known, the computer searches for the best fit of the particular amino acid sequence to that structure. Are the hydrophobic residues on the inside? Are the sequences with a strong propensity to form an α helix in an α helix? And so on. The best fit gets a numerical score reflecting the estimated stability of the structure.

In many cases, one particular three-dimensional structure will stand out as a good fit for the amino acid sequence, suggesting an approximate conformation for the protein domain. In other cases, none of the known folds will seem possible. By applying x-ray and NMR studies to the latter class of proteins, structural biologists hope to able to expand the number of known folds rapidly, aiming for a database that contains the complete library of protein folds that exist in nature. With such a library, plus expected improvements in the computational methods used for threading, it may eventually become possible to obtain an approximate three-dimensional structure for a protein as soon as its amino acid sequence is known.

Some Protein Domains, Called Modules, Form Parts of Many Different Proteins

As previously stated, most proteins are composed of a series of protein domains, in which different regions of the polypeptide chain have folded independently to form compact structures. Such multidomain proteins are believed to have originated when the DNA sequences that encode each domain accidentally became joined, creating a new gene. Novel binding surfaces have often been created at the juxtaposition of domains, and many of the functional sites where

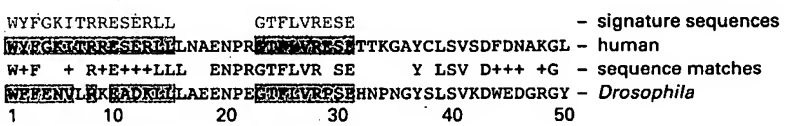

Figure 3–17 The use of short signature sequences to find homologous protein domains. The two short sequences of 15 and 9 amino acids shown *(green)* can be used to search large databases for a protein domain that is found in many proteins, the SH2 domain. Here, the first 50 amino acids of the SH2 domain of 100 amino acids is compared for the human and *Drosophila* Src protein (see Figure 3–12). In the computer-generated sequence comparison *(yellow row)*, exact matches between the human and *Drosophila* proteins are noted by the one-letter abbreviation for the amino acid; the positions with a similar but nonidentical amino acid are denoted by +, and nonmatches are blank. In this diagram, wherever one or both proteins contain an exact match to a position in the *green* signature sequences, both aligned sequences are colored *red*.